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ON THE PENETRATION OF SILVER
NITRATE AND OTHER ANTI-
GONORRHŒICS.

Some Experimental and Clinical Observations on the Value of the
Injection Therapy in Gonorrhœal Urethritis by
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FOR many generations silver nitrate held a dominant place in the therapy of the gonorrhœal affections of the mucous membranes. Long before the gonococcus had been discovered, and before any one had become aware of the bactericidal properties of the silver nitrate, that product had been recognised, empirically, as the sovereign remedy for the treatment of gonorrhœa. Simmons,¹ in 1786, was the first to introduce it in this branch of medical practice ; but it was Ricord² especially who, toward the middle of the last century, drew the serious attention of the whole medical world to its usefulness, and at whose recommendation it was taken up by nearly all the leading clinicians of the following decades ; in Denmark, for instance, by Engelsted,³ Bergh,⁴ and Erik Pontoppidan.⁵

In those days silver nitrate solutions were used, in cases of gonorrhœal urethritis in the male, partly as an ordinary injection treatment "on long sight," but partly also for the purpose of the so-called "abortive" treatment, the object of which was to cut short the infection by means of one or a few injections at most.

The concentrations used in those days were considerably stronger than what we are wont to employ nowadays. Two per cent. was the general strength ; and it is emphasised time and again, in the older literature, that the use of weaker solutions—which were tried, of course, on account of the excruciating pain and other discomforts resulting to the patient from the injection of a 2 per cent. lapis solution into the male urethra—makes for less reliable results and undue protraction of the treatment.

BRITISH JOURNAL OF VENEREAL DISEASES

The technique of the injection, too, was somewhat different from what we are generally practising nowadays. As a rule, a smaller quantity of fluid was injected, and was only retained for a very brief spell, and in most cases several days were let go between the individual injections.

To the modern physician this old treatment, with the highly concentrated solutions of the silver nitrate, must necessarily appear a drastic therapy indeed. When we think of its painfulness, and of its tendency to produce bleedings, strictures and other complications, it is almost beyond belief that it should have been possible to carry it through in normal, everyday practice. And yet, if we look over the results achieved by this seemingly barbarous method, we are forced to admit that, as a rule, they were surprisingly speedy and successful, both as regards the "abortive" treatment and in the cases where a more prolonged system of injections was used.

There is a remarkable contrast between the absolute agreement, voiced by all the older writers, concerning the excellence of silver nitrate as a remedy in gonorrhœa, and the therapeutic hesitations and divergencies that have marked the whole of the present era which was inaugurated fully thirty years ago under the slogan: *Organic silver compounds*.

The argonin, a silver caseinate, was probably the earliest of the countless preparations that dot the road of gonorrhœal therapeutics during all these years. It was introduced in 1895 at the recommendation of Jadassohn,⁶ and was followed ere long by numerous other more or less similar ones, like the protargol—which swam into favour upheld by the authority of Neisser⁷—albargin, largin, ichthargan, argentamin, and others too numerous to mention. More or less simultaneously with the introduction of these new remedies, the practice of more widely interspaced injections was abandoned, and the method was adopted of giving injections several times a day, each of as long duration as possible. In the beginning silver nitrate solutions, too, were used in this manner, for instance by Neisser, but only in strengths of from 0.5 to 2 per mille, on account of the frequency of the injections. But soon this remedy, though not entirely abandoned, was to a great extent at least superseded by the newly appeared organic silver compounds.

PENETRATION OF SILVER NITRATE

This alteration in the method of treating gonorrhœa was based on the following argument :

“ The great difficulty in antiseptising a gonorrhœa in the mucous membranes consists in obtaining from the antiseptic an action reaching sufficiently deep into those parts of the tissue, far below the surface, to which experience teaches us that the gonococci very speedily penetrate. It is therefore useless to employ silver nitrate, because that substance is almost immediately rendered inactive by being broken up into silver chloride and albuminates as a result of its coming into contact with the sodium chloride and albumen of the tissues. We must use silver compounds that will not be broken up by these substances, and which will thus preserve their quality of penetration.”

It is this argument which has prevailed absolutely during the whole of these thirty years, and of which has been born the host of organic silver compound preparations which has seen the light during all this period. And so seductive has this train of reasoning appeared to the whole venerologic world, without exception, that it has been clung to and pursued unswervingly—through argyrol, and choleval, and whatever the names of all these new preparations—in spite of all the deceptions experienced, and, strange to say, without a single person having, by the meagreness of the results, been tempted to cast as much as a shadow of doubt on the correctness of the basic principle asserted.

It is true that in the newer literature we occasionally find observations which show that the silver nitrate may now and then prove superior to the organic compounds. Scholtz,⁸ for instance, in the “ *Handbuch der Geschlechtskrankheiten*,” calls attention to this fact, which he thinks is due, however, to some particular action of the silver nitrate on the mucous membrane, independent of its disinfecting property. But to any criticism of the principle itself, the treatment of the gonorrhœa by means of organic silver compounds, those scattered observations have not given rise. That it should be a Danish critic who now ventures to raise his voice in opposition to this long and firmly established method is not merely accidental, however. For, as a matter of fact, it is precisely a Danish scientist, the Professor Rovsing,⁹ who, by his splendid results with the use of silver nitrate in cystitis, and by his demonstration of the bactericidal efficiency of

BRITISH JOURNAL OF VENEREAL DISEASES

the same substance when applied to the tissues, has furnished a basis on which these doubts might perhaps have been raised even before now. It was by the results of his observations, at all events, that the writer was actuated to undertake the investigations recorded in the following.

The first part of these investigations consisted in a perusal of the literature on the subject, merely for orientation, with a view to find out in what degree the organic silver compounds had answered the theoretical expectations formed of them. And right here it is curious to notice to what slight extent these new preparations have been thoroughly and systematically tested, after all, during these thirty years. The great majority of the serially tabulated investigations embrace no more than ten, or twenty, or thirty cases, and the judgment on these is generally based on the rapidity with which the gonorrhœal discharge is arrested and the time which it has taken for the gonococci to disappear ; while, as regards the one absolute criterion, namely, the definitive cure, the period of observation subsequent to the cessation of treatment has been, in most instances, utterly too short. There are, of course, a few collections of cases more extensive and more carefully observed, like the tabulation by Jersild,¹⁰ for instance, of 116 male cases of gonorrhœa treated with protargol ; but not even these present a very encouraging picture, when compared with the results obtained by the older school of venerologists with their lapis treatment. As a matter of fact, not one piece of clinical evidence has been forthcoming during all these years which would prove conclusively the superiority of the new remedies ; while, on the contrary, there is a curious disproportion between the results obtained by means of the—theoretically rather effective—silver nitrate and those achieved—or *not* achieved—by means of the supposedly so highly active, organic silver compounds. In any sober mind, this disproportion alone should suffice to arouse some very grave doubts concerning the validity of the theoretical considerations forming the basis for the modern method of treating gonorrhœa.

We have seen that penetration is the quality deemed important above all others, and therefore most particularly sought for, in the various preparations successively brought forward ; though, of course, it was aimed, at the

PENETRATION OF SILVER NITRATE

same time, to make them as strongly gonocidal as possible. But while numerous careful studies have been made of the various remedies with regard to the latter feature, the judgment concerning their penetrative powers has generally been allowed to rest on merely theoretical assumptions; the actual experiments in that direction are few and not particularly convincing.

Schaefer¹¹ studied the penetration effect by placing pieces of liver for ten hours in 0.5 per cent. solutions of silver nitrate and in argentamin solutions of similar strength. By afterwards precipitating the absorbed silver by means of ammonium sulphite, he was able to ascertain that the argentamin penetrated about three times as deeply as the silver nitrate. Similar experiments were made by Pezzoli¹² with silver nitrate, argentamin, protargol and largin, with the result that to a penetration, for argentamin, of 100, there corresponded: for silver nitrate, 65; for largin, 58; and for protargol, 38. Benario¹³ made stab cultures, in agar, of various bacteria, and poured over them a 0.5 solution of protargol, whereupon he was able to demonstrate that a zone of from 12 to 13 mm. remained sterile. Another, somewhat similar experiment was made by Pezzoli by means of four test-tubes containing nutrient gelatin to which had been added a little *B. coli* culture. Into each of the tubes he poured a different silver solution, covering the gelatin to the same height; here also the establishment of a sterile zone was the result: for the argentamin to a depth of 16 mm., for the silver nitrate to 4 mm., for the largin to 10 mm., and for the protargol to 5 mm. in depth. Blumberg¹⁴ studied the effect on the spleen of mice which he had infected with anthrax and *micrococcus tetragenus*. He exposed pieces of the spleen for varying lengths of time to different disinfectants, which he afterwards removed again as far as possible by rinsing, subsequently inoculating the torn-out fragments of tissue. By this proceeding he found the argentamin to have the deepest penetration, followed, in the order named, by actol, itrol, silver nitrate and argonin.

Against the validity of these tests a number of objections have been raised, the most important one being that the conditions of them are so greatly at variance with those of actual, therapeutical application. It has, therefore, been tried also to attack the problem in another fashion,

BRITISH JOURNAL OF VENEREAL DISEASES

namely, by microchemical observations on the live mucosa, and especially on the membranes of the urethra and the conjunctiva. In this manner the penetration of the various silver solutions has been investigated, for instance, by Casper,¹⁵ Von Ammon,¹⁶ Calderone,¹⁷ Aisinmann,¹⁸ and Lohnstein.¹⁹ The results arrived at by these investigators do not agree completely; still, the majority of them seem to show that it is the silver nitrate which possesses the greatest power of penetration. Langer and Jacobsohn,²⁰ in a recently published communication, state that, by experiments of a similar kind, undertaken on the urethras of dead bodies, they, too, have found the greatest penetrative power in the silver nitrate, with albargin, protargol and choleval following in the order named.

My own method for the experimental investigation of this important problem was very similar to the one employed by Pezzoli, of test-tubes containing gelatin and bits of *B. coli* culture; the only difference being that to the gelatin I add a certain quantity of ascitic fluid, in order to increase as far as possible the likeness to the conditions actually obtaining in the mucous membrane. It is only right to point out, however, that, in spite of this, the differences between experiment and actual conditions are, of course, far too great to allow of any absolutely binding conclusions being made by analogy from the one to the other. Still, we can at least by these means get an insight into certain fundamental conditions pertaining to the various silver compounds and their manner of reacting when brought into contact with albumen and NaCl, and we are able to obtain in relative terms a measure, by no means unimportant, of their power of penetration.

The details of my technique were as follows:—Test tubes of equal diameter were filled to the same height with nutrient gelatin, to which had been added 33 per cent. of ascitic fluid and a small quantity of *B. coli* culture. When the gelatin had coagulated there were poured over it equal quantities of the various solutions to be tested, a different kind to each tube. The tubes were then placed in the refrigerator for eighteen hours. Afterwards they were left for forty-eight hours at room temperature, during which time the bacilli developed, forming a diffuse cloudiness in the medium. Thereupon the depth of the sterile zone in the upper part

PENETRATION OF SILVER NITRATE

of the gelatin was measured, a performance which presents no difficulty, inasmuch as the upward limit of the bacterial growth is, as a rule, quite sharply defined. Under like conditions of testing the differences are very small, rarely exceeding 1 mm. On the other hand, there is, of course, always a certain variation between the results obtained in the different series of experiments, principally because the depth to which a given solution will arrest the bacterial growth depends to a great extent on the quantity of bacteria sown, and on the greater or lesser vitality, or "energy for growth," possessed by those particular bacteria. Comparisons must, therefore, be limited to experiments made within one and the same series. That neither the diameter of the test tubes used, nor the greater or lesser height of the gelatin column in the tubes, has any noticeable influence on the results obtained was ascertained beforehand by experiments made for this express purpose. Nevertheless, all the tests referred to in the following were, of course, made under conditions exactly similar, both as regards the size of tubes and the quantities of gelatin employed.

Of the results obtained by this method, I will mention first the ones having reference to the silver nitrate. The initial experiments were undertaken with concentrations of 2 per mille and less; and right here there appeared the curious fact that the greatest penetration was not—as one would naturally have expected—produced by the most highly concentrated solution, but that the maximum of penetration was registered for solutions of about $\frac{1}{10}$ per mille strength. Tables I., II. and III. show the drop in the penetration figures to both sides from this point.

TABLE I.—PENETRATION OF SILVER NITRATE IN 33 PER CENT. ASCITES-GELATIN.

| Concentration in per cent. of AgNO ₃ | 2 | 1 | $\frac{1}{2}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{16}$ | $\frac{1}{32}$ | $\frac{1}{64}$ | $\frac{1}{128}$ | $\frac{1}{256}$ |
|--|-----|-----|---------------|---------------|---------------|----------------|----------------|----------------|-----------------|-----------------|
| I. | 2.0 | 2.5 | 3.5 | 4.5 | 5.0 | 4.5 | 4.5 | 3.0 | 2.5 | 1.5 |
| Penetration in mm. II. | 3.5 | 4.5 | 4.0 | 4.5 | 5.0 | 7.5 | 6.0 | 3.0 | — | — |
| III. | 2.5 | 3.5 | 4.5 | 5.0 | 6.0 | 6.0 | 6.0 | 5.5 | 4.5 | — |

The curious conditions here observed would seem, from all indications, to be due to a distinct peculiarity of the

BRITISH JOURNAL OF VENEREAL DISEASES

precipitated silver chloride. That the silver nitrate solution can have any bactericidal effect at all, for a certain distance downward into the gelatin, can only be accounted for by supposing that the precipitation of the silver is not complete, but that a certain portion of it remains in solution, under one form or another, and is diffused downwards into the medium. One may conjecture here the formation of some soluble silver albuminate, and may remember also the well-known fact that silver chloride itself is not absolutely insoluble, particularly when other chlorides are present. I have examined the first of these possibilities by making a number of tests with gelatin containing ascitic fluid in various proportions. If soluble metal albuminates were the determining factor, it might reasonably be expected that a lessening in the albumen content would result in the bactericidal effect becoming equally less; but as will be seen from Table II., it is precisely the contrary that is the case. On the whole, there is a slight diminution in the downward effect, as the content of ascitic fluid is increased and probably due to the active substance becoming adsorbed to the albumen. And the optimum for the penetration remains almost invariable for the same concentration.

TABLE II.—PENETRATION IN MILLIMETRES OF SILVER NITRATE UNDER VARIOUS CONDITIONS OF PROPORTION BETWEEN THE ASCITIC FLUID AND GELATIN CONTENTS IN THE TUBES.

| Concentration in per cent. of AgNO ₃ | $\frac{1}{2}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{16}$ | $\frac{3}{32}$ | $\frac{1}{64}$ | $\frac{1}{128}$ | $\frac{1}{256}$ | $\frac{1}{512}$ | $\frac{1}{1024}$ |
|---|---------------|---------------|---------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|------------------|
| 33 per cent. ascitic fluid | 5.5 | 3.5 | 5.0 | 6.5 | 7.0 | 7.0 | 8.0 | 6.5 | 5.5 | 4.5 |
| 8 per cent. ascitic fluid | 4.5 | 4.5 | 6.5 | 8.5 | 8.5 | 9.0 | 9.0 | 8.5 | 8.0 | 7.0 |
| No ascitic fluid . . . | 4.5 | 4.5 | 8.5 | 10.5 | 11.0 | 11.5 | 11.0 | 10.0 | 9.5 | 9.5 |

It seems more reasonable, therefore, to seek the explanation of this effect in the silver chloride. Now, in the concentrations with which we have been dealing so far, there is this peculiarity about the precipitation of the silver chloride, that it takes place altogether and exclusively in the fluid above the gelatin, while within the gelatin there is no trace whatsoever of any precipitation. If, therefore, the bactericidal action is really due to the silver chloride, it must probably be because some

PENETRATION OF SILVER NITRATE

portion of the latter becomes dissolved and diffuses itself downward into the coagulated medium. It is a well-known fact, however, that the consistency of the silver chloride is very diverse, according to the concentration of the solution from which it is separated out, highly concentrated silver nitrate solutions giving a compact, or even crystalline sediment, while the more strongly diluted ones give a more finely divided precipitate, or even hold the silver chloride in suspension in colloid state. And, as it has been shown by Stas,²¹ the solubility is considerably greater for substances in the latter forms; therefore the fact that, under certain circumstances, weak solutions of silver nitrate produce a stronger effect than the more highly concentrated ones, can in reality be explained by the relatively greater number of silver ions that are held in suspension in the former, with resulting possibility of becoming diffused downward into the medium.

That this is, in fact, the true explanation is proved by the experiment recorded in the following table (Table III.), which shows, in the first place, the penetration of silver nitrate, and, in the second place, the penetration of silver chloride previously separated out from the same silver nitrate concentrations with an equivalent quantity of NaCl. It will be observed that the results are almost identical, whether silver nitrate be used, or equivalent quantities of emulsioned silver chloride. At the same time the differences in the consistency of the silver chloride can be directly observed in these experiments, where it is noticed that, in the higher concentrations, it forms a compact sediment on top of the gelatin column, leaving the rest of the liquid absolutely clear; while, in the weaker concentrations, the whole of the liquid above the gelatin is of a diffuse, opalescent, cloudy appearance.

TABLE III.—PENETRATION OF SILVER NITRATE COMPARED WITH THE PENETRATION OF SILVER CHLORIDE PRECIPITATED FROM EQUIVALENT SOLUTIONS.

| Concentration in per cent. of AgNO ₃ . | $\frac{1}{2}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{18}$ | $\frac{1}{32}$ | $\frac{1}{64}$ | $\frac{1}{128}$ | $\frac{1}{256}$ | $\frac{1}{512}$ | $\frac{1}{1024}$ |
|---|---------------|---------------|---------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|------------------|
| Penetration in mm. of AgNO ₃ | 5.5 | 5.5 | 7.5 | 9.5 | 10.0 | 10.5 | 10.0 | 9.5 | 9.0 | 8.0 |
| Penetration in mm. of AgCl | 7.0 | 8.0 | 9.5 | 10.5 | 10.5 | 9.5 | 10.0 | 9.0 | 8.5 | 8.0 |

BRITISH JOURNAL OF VENEREAL DISEASES

When experiments are made with silver nitrate solutions more highly concentrated than the ones hitherto mentioned, it is found that, from a certain point onward, the deep-effect begins to increase once more, becoming stronger and stronger with increased concentration. At about the point of concentration where this change takes place a precipitation of silver chloride begins to be noticed in the uppermost layer of the gelatin, and this column of precipitated silver chloride becomes higher and higher with increased concentration of the silver nitrate solution. At the same time the sterile zone below this column of silver chloride becomes more and more shallow as the concentration is increased, a circumstance which accords very well, of course, with the lesser solubility of the silver chloride formed. The change referred to occurs at about $\frac{1}{2}$ per cent. AgNO_3 , which corresponds about to the point where the NaCl in the gelatin equals AgNO_3 in the solution. If more NaCl is added to the gelatin, the precipitation in the latter will begin only with the use of correspondingly higher concentrations of AgNO_3 , and the columns of silver chloride become smaller than otherwise. Table IV. shows a series of these experiments, and gives a clear idea of the curious manner in which the penetration of the silver nitrate becomes increasingly less as the concentration is reduced from the higher strengths to about 1 per mille; followed by an increasing power of penetration for solutions down to $\frac{1}{10}$ per mille, when there is another, and this time steady, reduction of the deep-effect produced.

TABLE IV.—PENETRATION OF SILVER NITRATE IN 33 PER CENT. ASCITES-GELATIN.

| Concentration in per cent. of AgNO_3 . | 30 | 10 | 5 | 2 | 1 | $\frac{1}{2}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{16}$ | $\frac{1}{32}$ | $\frac{1}{64}$ | $\frac{1}{128}$ |
|---|---------------|---------------|------|------|-----|---------------|---------------|---------------|----------------|----------------|----------------|-----------------|
| Penetration in mm. . . | approx. 25 | approx. 19 | 14.5 | 10.0 | 8.0 | 5.0 | 4.5 | 5.5 | 6.0 | 7.5 | 6.5 | 6.5 |

The curious fact that a precipitation of silver chloride takes place in the medium of diffusion itself at one particular concentration of the silver nitrate solution while, with lower concentrations, there is no indication whatever to the same effect, is a circumstance which

PENETRATION OF SILVER NITRATE

ought undoubtedly to be made a note of when it comes to the question of using the substance for therapeutical purposes. If, for example, this same condition is found to obtain as far as the live tissue is concerned—and there is every reason to believe that such is the case—it means, of course, that only the relatively strong lunar caustic solutions, of about 1 per cent. strength and upwards, will be capable of producing the deposition of silver chloride in the tissues and, thus, of ensuring a continued effect; while the action of the weaker solutions will probably only be that which is produced by the dissolved silver chloride itself. The extent of this latter action depends, however, as proved by Gros,²² on the quantity of undissolved silver chloride formed, because, with all other conditions equal, the effect will increase in proportion to that quantity. This is perhaps the explanation also of the decreasing penetration observed when only very weak solutions are used, though the latter are still saturated, of course, with dissolved silver chloride. It is impossible not to view the matter thus on the background of the firm adherence of the old-time clinicians to the 2 per cent. lapis solution for gonorrhœa, and of Roving's treatment of cystitis with solutions equally as strong. This is a case where experiment supports the clinically well-founded confidence in those therapeutical methods.

On the other hand, the result of the experiments shows the error of simply taking for granted that, in the case of the weak lapis solutions, the power of penetration increases with the strength of the solution. On the contrary, as we have seen, the optimum of deep-effect seems to lie at a rather low concentration. It is, therefore, very likely that our present way of treating an anterior gonorrhœa—with silver nitrate solutions of from $\frac{1}{4}$ to $\frac{1}{3}$ per mille strength, and tentative increases of the concentration as far as can be done without irritating the mucosa—is wrong, at least in principle, because the optimum of concentration, as far as deep-effect is concerned, may with perfectly good reason be thought to lie farther down, though, of course, it need not correspond just exactly to the one found in the test tube. An entirely different thing is that, in all probability, the higher concentration increases the bactericidal effect as far as the surface is concerned; but to secure this at the cost of

BRITISH JOURNAL OF VENEREAL DISEASES

a lessened deep-effect would undoubtedly in most cases be a very doubtful advantage.

That we should ever come back to the old, drastic 2 per cent. lapis treatment for anterior gonorrhœa is out of the question. But the experimental results here recorded might serve as the basis for a further therapeutical investigation comprising the treatment of a sufficient number of cases by weak silver nitrate solutions, in various dilution, but of constant strength within each separate series of experimentation, with a view to finding, if possible, the exact optimum of concentration for the treatment of that disease.

The results arrived at by the experiments here communicated prove the error of the general conception of the silver nitrate as an agent incapable of producing any beyond a mere superficial effect. At least in media containing albumen and sodium chloride there is a possibility of bactericidal effect from the silver nitrate, even at rather considerable depths, and, curiously enough, it is on the very process which was supposed to be the greatest bar to it—namely, the formation of silver chloride—that the power of penetration depends.

The next question is : How does the penetrative power of the silver nitrate compare with that of other silver compounds, and more especially with the penetration of those which do not precipitate either chlorides or albumen ?

All the investigations hitherto undertaken for the purpose of elucidating this point suffer from the common defect that the experiments have been made with only one strength of concentration of the substances tested ; for the silver nitrate, for instance, usually in a strength of 1 per mille, which, as we have seen, is about the most unfavourable concentration of all for that substance. There was, therefore, every reason to undertake a fresh series of experiments of this kind on a more extensive scale and with various concentrations.

By thus examining a number of these other silver compounds—with employment of the same technique as for the silver nitrate—I found, in respect to several of them, conditions precisely similar to those observed as characteristic of the latter substance, namely, an increase of penetration following the ratio of dilution down to a

PENETRATION OF SILVER NITRATE

certain point, after which the penetration again became less as the dilution proceeded. On the other hand, I did not find in any of these compounds the same increase of penetrative effect from very strong concentrations that was manifest in the case of the silver nitrate.

To this group belong the following preparations, for each of which I have indicated here the strength of concentration producing the maximum of penetration :—

| | | | | | | | |
|-----------|---|---|---|----------------|----|-----------------|-----------|
| Actol | . | . | . | $\frac{1}{64}$ | to | $\frac{1}{128}$ | per cent. |
| Itrol | . | . | . | $\frac{1}{40}$ | ” | $\frac{1}{80}$ | ” |
| Protargol | . | . | . | $\frac{1}{4}$ | ” | $\frac{1}{8}$ | ” |
| Albargin | . | . | . | $\frac{1}{2}$ | ” | $\frac{1}{4}$ | ” |
| Choleval | . | . | . | $\frac{1}{4}$ | ” | $\frac{1}{8}$ | ” |

For reasons of “space economy” I confine myself to tabulating only a couple of the experiments with protargol, which will show the great differences in deep-effect of the various concentrations. The ratio of these differences was about the same for all the compounds here mentioned.

TABLE V.—PENETRATION OF PROTARGOL IN 33 PER CENT. ASCITES-GELATIN.

| Concentration in per cent. of protargol. | | 4 | 2 | 1 | $\frac{1}{2}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{16}$ |
|--|-----|-----|-----|-----|---------------|---------------|---------------|----------------|
| Penetration in mm. | I. | 2.0 | 2.5 | 3.0 | 4.0 | 5.0 | 4.5 | 4.5 |
| | II. | 3.5 | 4.0 | 4.0 | 5.0 | 6.0 | 5.0 | 4.0 |

The striking parallelism in these respects between the organic argentous compounds thus examined and the silver nitrate naturally led to the question whether the relation between cause and effect might not be the same in all of them: ascribable to the formation of silver chloride and to the action produced by a small portion of the latter becoming dissolved and diffused downward into the gelatin.

As regards the actol and the itrol it is very probable that such is the case, inasmuch as they both by NaCl become precipitated as silver chloride, and in the experiments give results exactly similar to those obtained with the silver nitrate. As regards the protargol, the albargin and the choleval, the problem is somewhat more complex, from the fact that these compounds are stated to be more constant in the presence of NaCl. It is found,

BRITISH JOURNAL OF VENEREAL DISEASES

however, that even these argentous compounds, when left with NaCl for any considerable length of time, will little by little form AgCl, the latter appearing first as an opalescent cloudiness, and later as a distinct sediment giving all the reactions of silver chloride. This circumstance—the importance of which, as regards the bactericidal possibilities of these substances in media containing sodium chloride, has been called attention to by Gros—appears with particular distinctness in the diffusion experiments, where silver chloride, in a more or less finely divided state, is formed in the column of liquid above the gelatin.

That the compounds mentioned are thus precipitable with chlorides, even if this reaction is a very slow one, can be explained only on the theory that a portion of their silver content is present in the form of free silver ions. But that even rather considerable quantities of such free silver ions are present in many organic silver preparations has already been conclusively demonstrated by Von Neergaard,²³ who has shown that in albargin 64 per cent. of the silver is dissociated, and in protargol 28 per cent. And when these solutions are not immediately precipitated by the chlorides it is probably because the organic component of the preparation acts as a protecting colloid, holding the silver chloride suspended for a considerable length of time in a colloidal state.

Among the silver compounds there are a certain number that do not have the same characteristic maximum for deep-effect at a certain, rather low concentration, as the silver nitrate and the various preparations belonging to the above-named group. These are, in the first place, the complex silver compounds: potassium silver cyanide, silver chloride dissolved in sodium thiosulphate, and silver chloride dissolved in thiocarbamide. Of all these the penetration becomes more effective with increased concentration; but the bactericidal effect is so small—owing to the very small quantities of free silver ions given off by them—that very often the inhibition in the zone of diffusion is not complete. Similar characteristics are shown by the two compounds, argyrol and argentamin, which are both rather extensively employed for therapeutic purposes. In neither of these, either, does any precipitation of silver chloride take place, even slowly, and it is probably this failure to precipitate that accounts

PENETRATION OF SILVER NITRATE

for the different behaviour of this whole group as regards penetration.

Thus, in the matter of deep-effect, the silver compounds divide themselves into two large groups: one in which the maximum of that effect is obtained with a rather low concentration, and another in which the deep-effect seems to become stronger with increased concentration. It is within the first of these two groups that we find the most commonly employed antigonorrhœics, and a comparison between these, in their respective optima of concentration, with those of the second group in the strength serviceable for therapeutic purposes, gives some rather interesting results, which will be seen from the following table (Table VI.) :—

TABLE VI.—COMPARATIVE EXPERIMENTS ON THE PENETRATION OF DIFFERENT SILVER COMPOUNDS IN 33 PER CENT. ASCITES-GELATIN.

| Concentration, in per cent. | | AgNO ₃ | | Protargol | | Albargin | | Choleval | | Argentamin | | | Argyrol | | | |
|-----------------------------|------|-------------------|-----------------|---------------|---------------|----------------|----------------|---------------|---------------|---------------|----------------|----------------|---------|-----|---------------|---------------|
| | | $\frac{1}{84}$ | $\frac{1}{128}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{20}$ | $\frac{1}{40}$ | $\frac{1}{4}$ | $\frac{1}{8}$ | $\frac{1}{2}$ | $\frac{1}{10}$ | $\frac{1}{20}$ | 2 | 1 | $\frac{1}{2}$ | $\frac{1}{4}$ |
| Penetration in mm. | I. | 7.5 | 6.0 | 6.0 | 5.0 | 7.0 | 4.5 | 4.0 | 4.0 | 6.0 | 5.0 | 4.5 | — | — | — | — |
| | II. | 7.0 | 7.5 | 6.0 | 5.5 | 7.0 | 7.0 | 5.5 | 5.0 | — | — | — | — | — | — | — |
| | III. | 8.0 | 7.5 | 6.0 | 6.0 | 7.0 | 6.5 | 4.0 | 5.0 | — | — | — | 10.0 | 8.5 | 5.5 | 3.0 |

We see here that the silver nitrate leads among the substances in Group I. As regards the substances in Group II., it will be possible to obtain an even stronger deep-effect, at least with both the argyrol and the complex silver compounds in therapeutically serviceable concentrations; but, as already stated, we can in most cases count only on a minimum of bactericidal effect from these preparations, in which the dissociation is so slight, and the precipitation, for this reason, practically *nil*.

The most noticeable fact brought out by these comparative tests is the relatively considerable penetration of the silver nitrate. The demonstration of this does not prove, of course, that the silver nitrate is superior, also in practice, to such other remedies as protargol and albargin. But it shows at least that, experimentally, the theoretical basis for the disparagement of the silver nitrate in favour of the newer preparations—namely, the argument of its supposed incapacity for penetration owing

BRITISH JOURNAL OF VENEREAL DISEASES

to precipitation of the silver chloride—does not hold good at all.

The experimental results being as described in the foregoing, it would seem absolutely indicated to examine whether *the clinical results*—which constitute, of course, the court of last appeal in cases like this—would really prove the protargol, the albargin and the rest of the new preparations to be superior to silver nitrate. Strange to say, it is only to a very limited extent that clinical research has occupied itself with this question so far, and for reasons which I have already mentioned in the foregoing it is impossible to form any reliable judgment on the basis of the results come to by previous investigators.

For a comparative investigation of this kind to have any value, it is necessary, in the first place, that the whole of the material on which the comparisons are based should have its provenance from the same clinic and should be of exactly the same character, just as the whole technique of injection, instruction and advice to the patients, etc., must be absolutely uniform, in such a manner that there is no variation except as regards the remedy employed.

From the Policlinic for Skin and Venereal Diseases of the Rigs Hospital at Copenhagen I have made a collection of cases strictly fulfilling the conditions here enumerated, and of which it should further be added that (1) only fresh, previously untreated cases of primary male gonorrhœa with clear second urine were included; (2) only those cases were counted in for which a three weeks' period of observation after the end of treatment could be established; and (3) no case was set down as "cured" unless, during that period, there had been a complete absence of even the slightest sign of relapse.

Such rigorous conditions necessarily make for a considerable reduction of the material numerically, but, on the other hand, they present a great many advantages. Thus by excluding all cases of posterior urethritis we become sure of operating only with cases in which there is a full possibility of the injection treatment getting to act on the whole of the infected area; and to eliminate in the same manner all cases of secondary and subsequent gonorrhœas is the only sure way of preventing the inclusion in the observation material of relapse cases, of which we know that they generally take a much more favourable course than the fresh infection. It is true

PENETRATION OF SILVER NITRATE

that the three weeks' period of observation does not present any absolute guarantee of a cure ; still, practical experience makes it permissible to regard it as a sufficiently safe criterion for the purposes of comparative research.

To the appreciation of protargol, albargin and silver nitrate I have been able to make observations based on 50 cases for each substance. The protargol was employed in strengths increasing from $\frac{1}{4}$ to $\frac{1}{3}$ per cent. ; the albargin in strengths from $\frac{1}{2}$ to 2 per cent. ; and the silver nitrate in strengths from $\frac{1}{8}$ to $\frac{1}{3}$ per mille. The treatment consisted of three injections per day, and the patients were instructed to retain the injected liquid for five minutes. They were further instructed to micturate immediately before each injection, and to refrain from micturition for as long a time as possible afterwards. Of the cases making up my tabulated material, the treatment has been carried through without change of the remedy once begun with, except in those instances where it was found that it took an undue time to bring about a cure. In those cases (they are the ones figuring in the fourth column of Table VII.) it was necessary to make a change

TABLE VII.—150 CASES OF GONORRHOEA (1 ACUTE ANTERIOR): 50 TREATED WITH PROTARGOL, 50 WITH ALBARGIN, 50 WITH SILVER NITRATE.

| | | | | | Complications in course of the Treatment. | | |
|---------------------|-----|-----|------|------|---|--------------|--|
| | | | | | Epididymitis. | Prostatitis. | Other complications except urethr. post. |
| Cured after weeks : | < 4 | 4-8 | 8-12 | > 12 | | | |
| Protargol . . . | 1 | 9 | 18 | 22 | 3 | 5 | 0 |
| Albargin . . . | 1 | 6 | 13 | 30 | 4 | 5 | 1 |
| Silver nitrate . | 2 | 16 | 15 | 17 | 3 | 2 | 1 |

of remedy ; but it is evident that they are of the kind in which the chance of a cure being effected by merely local treatment was altogether highly problematical. Cases of that character can, as a matter of fact, give only very little positive information regarding the action of a remedy. It is on the indications furnished by the cases in which the cure is relatively swift that we must rely

in this respect, because these are the only ones of which it can with a fair degree of certainty be concluded that it is really the injection therapy adopted which has been the decisive factor in bringing about the cure. Table VII. shows the results of this comparative investigation. The complications with posterior urethritis are not added up, because of the necessary uncertainty attaching to a correct estimation on this point.

We see here that the results from protargol and albargin are more or less similar, while the silver nitrate gives a greater number of cases for the group of relatively speedy cures. Also if we look at the complications the figures are rather in favour of the last-named substance.

It should be remarked that the treatment of the greater number of these cases had been commenced before I had undertaken the tube tests described in the foregoing pages, and that, therefore, the possibility of these tests having in any way influenced the clinical results here recorded—through some particular interest and care having been given to the silver nitrate cases—is absolutely precluded.

The fact of the matter is, that the clinical results speak the same language as the diffusion tests, but absolutely independently of the latter, and that the pronouncement of them both is in favour of the silver nitrate. This circumstance in itself should, of course, aid considerably in strengthening our confidence in the diffusion tests as a guiding line for the therapeutical practice, and the only question remaining is, whether the paramount importance of proper concentration revealed as the principal condition of penetration in the tubes will have its corollary also as regards the conditions in the urethral mucosa. In the cases tabulated above—which, as stated, were treated, for the greater part, before I had any knowledge of the experimental results here referred to—the concentration of the remedies has been increased in the usual manner, little by little, in the course of the treatment. But it is highly possible, of course, that for the mucous membrane, as for the gelatin, the optimum of penetration coincides with a certain definite degree of concentration of the substance employed. It may not be precisely the same degree of concentration as the experimental one; nor is it absolutely certain that the optima for deep-effect and curative effect are precisely identical; still, it is

PENETRATION OF SILVER NITRATE

probable that some definite degree of concentration will prove to be the best therapeutically, and in that case it will, of course, be fundamentally a mistake to operate with a gradual increase of the strength of the solutions. To determine the optimum of concentration for action on the urethral mucosa will, of course, only be possible through an extended series of clinical investigations. This work has been commenced, but it is evident, from the nature of the task itself, that a considerable time will elapse before a sufficiently large material shall have been collected to make possible a definite, authoritative pronouncement on this point. From present indications it would seem that the best results are obtained with silver nitrate solutions of $\frac{1}{5}$ per mille strength ; but, as yet, it is impossible to say with any degree of certainty whether these results will be to any noticeable extent better than the ones already described.

By means of diffusion experiments we shall also be able to investigate whether it is possible to increase the penetration by the addition of various substances to the silver solutions. In a previous paper I²⁴ have communicated some results of treating gonorrhoea by protargol to which alcohol had been added. Among the cases referred to in that connection there were a number of very rapid cures, but it is true that these successes were offset by an excessive delay in effecting a cure in a number of others. I have carried out some diffusion experiments with such alcoholic protargol solutions, but the deep-effects registered were by no means greater than from the solutions with water. That their efficacy can possibly nevertheless be stronger may perhaps be explained by the fact—which has been demonstrated by Eisenberg, Okolska,²⁵ and Th. Hansen²⁶—that the bactericidal effect of a good many substances is increased by the addition of alcohol. But besides alcohol there are, of course, numerous other substances which it would be of interest to test ; and possibly a combination of diffusion tests with investigations into the bactericidal effects might result in our lighting on some substance which would still further increase the efficacy of the best silver compound—presumably the silver nitrate—in the most effective strength of concentration.

However much all this may be “ music of the future,” the fact remains that the results of both the experimental

BRITISH JOURNAL OF VENEREAL DISEASES

and the clinical investigations prove the injustice of the silver nitrate having been relegated out of the gonorrhœal therapy in favour of the organic silver compounds. Both in the test tubes and by the compared results of clinical treatment the old "lapis infernalis" has, in fact, shown itself not only the equal of, but even superior to, the newer preparations.

There is, therefore, every reason to restore the silver nitrate to the leading place among antigonorrhœics which was accorded to it by the clinicians of an older generation, and from which it was expelled, not owing to any experimental or clinical demonstration of its inferiority, but in reality to the strength of an argument which has now, both experimentally and clinically, been proved untenable. If the silver nitrate is to be set aside in favour of one or another among the scores of preparations for the cure of gonorrhœa that have already seen the light during the last thirty years, and of which new ones are sure to be launched in the days to come, it must at least be demanded that the superiority of these new remedies should be proved by means of comparative tests. It is by no means sufficient to point in their favour to a particular rapidity of action on the gonococci or in the matter of arresting the discharge. It is the definite cure that matters, and if this cannot—in the great general run of cases—be obtained more quickly by means of the new remedy than by employing the silver nitrate, there is absolutely no reason why this simple, cheap and well-known preparation should be discharged in favour of some complicated, expensive and unknown patent preparation.

SUMMARY

There is no reliable basis, either experimental or clinical, for supposing organic silver preparations to be more efficacious than silver nitrate as a remedy for use in the injection treatment of gonorrhœa.

Diffusion tests with silver nitrate, in ascites-gelatin sown with *B. coli*, show that substance to possess a rather considerable power of penetration, as measured by the depth to which inhibition is produced. The relation of the concentration-strength of the solutions employed to the deep-effect produced shows some very curious features. From a maximum of penetration obtained by highly concentrated

PENETRATION OF SILVER NITRATE

solutions this deep-effect falls to a minimum at a concentration of about $\frac{1}{4}$ per cent. strength, whence it rises again for concentrations up to about $\frac{1}{10}$ per mille strength; from which point onward there is a renewed and steady decline in the deep-effect produced.

That the penetration can become deeper with increasing dilution is probably due to the circumstance that the solubility of the precipitated silver chloride becomes greater, the weaker the silver nitrate solution from which it is separated out.

That the penetration increases again for the higher concentrations of the silver nitrate is probably due to the fact that with these higher concentrations precipitation of silver chloride takes place in the gelatin itself, while with the weaker solutions all the silver chloride remains in the liquid above the coagulated gelatin. This reversion in the principle of precipitation occurs at a definite degree of concentration, which is determined, however, by the amount of NaCl contained in the gelatin, in the sense that the point of reversion is displaced upwards when the NaCl content is increased.

An "effect by deposition" from the silver nitrate can, therefore, probably be obtained only by employing solutions of about 1 per cent. strength, or higher. If weaker solutions have to be used, the very weak ones will give greater possibilities for penetration than solutions of medium weakness.

Of other silver compounds, protargol, albargin, choleval, itrol and actol behave on lines essentially similar to the ones observed as characteristic of the silver nitrate, the maximum of penetration of these compounds also coinciding with a rather low degree of concentration. The penetration of the complex silver salts, on the other hand, as well as of argyrol and argentamin, increases with higher concentration.

Comparative tests of the deep-effect produced, respectively, by silver nitrate and by the organic compounds of the first group, in their respective optima of concentration, show the silver nitrate to have the greatest power of penetration. With argyrol and the complex silver salts a still greater deep-effect can be obtained from concentrations of therapeutically serviceable strength, but the bactericidal efficacy of those substances seems to be slight.

The results of comparative clinical tests with silver

BRITISH JOURNAL OF VENEREAL DISEASES

nitrate, protargol and albargin, based for each of these remedies on the treatment of 50 distinct cases of acute, uncomplicated primary anterior gonorrhœa (male), spoke distinctly in favour of the silver nitrate as the best.

There is thus every reason why the silver nitrate should be adhered to as the standard remedy to be used in the injection treatment of gonorrhœa. In those situations—the female urethra and the male posterior urethra—where stronger solutions can be used without too much discomfort to the patient, the results of the experiments point to solutions of 1 per cent. strength, or higher, as the optimal concentration; in fact, the stronger the better. Where it is necessary to use weaker solutions—as in the male anterior urethra—the experiments would seem to indicate that the greatest penetration is obtained from a definite, rather low degree of concentration. It is, therefore, possible that the usual procedure of gradually increasing the concentration as the treatment proceeds is fundamentally wrong. It undoubtedly increases the bactericidal effect as far as the surface is concerned; but this would be done then at the cost of a lessened effect farther down in the tissues. Further clinical, comparative studies should be made with a view to find out precisely which concentration gives the best result in the average case, and the treatment should then, as a matter of general routine, be restricted to solutions of that particular strength. This does not mean, of course, that in refractory cases it might not be advisable to vary the concentration; but there would then be just as good, or rather better, reason to try with weaker solutions than with more highly concentrated ones.

BIOGRAPHY

- (1) SIMMONS. *Cit. i Finger. Blenn. der Sexualorg. Lp.*, 1893, p. 122.
- (2) RICORD. *Traité des mal. vén.*, Paris, 1838.
- (3) ENGELSTED. *Klin. Vejl. til Diagn. Bhd. og Forebyggelse af ven. Sygdom. Kbhvn.*, 1877, p. 374.
- (4) BERGH. *Bidrag til Kundsk. om Gon. hos Mandfolk, Kbhv.*, 1860, p. 60.
- (5) PONTOPPIDAN, E. *Terap. Medd., Kbhvn.*, 1891.
- (6) JADASSOHN. *A. f. D. and S.*, 1895, B. 32, p. 179.
- (7) NEISSER. *Derm. Zentr. bl.*, 1897, B. 1, p. 3.
- (8) SCHOLTZ. *Handb. d. Geschl. Krankh.*, 1910, B. 1, p. 520.
- (9) ROVSING. *Om Blæretændelsernes Ætiologi, Pathog. og Behandl. Kbhv.*, 1889.

PENETRATION OF SILVER NITRATE

- (10) JERSILD. *U. f. L.*, 1913, p. 961.
- (11) SCHÄFFER. *Münch. med. W.*, 1895, p. 641.
- (12) PEZZOLI. *Wien. klin. W.*, 1898, p. 260.
- (13) BENARIO. *Deutsche med. W.*, 1897, *Terap. Beilage*, p. 82.
- (14) BLUMBERG. *Diss.*, Breslau, 1897.
- (15) CASPER. *Diss.*, Berlin, 1897.
- (16) v. AMMON. *Münch. med. W.*, 1900, p. 12.
- (17) CALDERONE. *Giorn. ital. d. mal. ven. e della pelle*, 1905, p. 5.
- (18) AISINMANN. *Deutsche Artztez.*, 1913, *cit. Handb. d. Geschl. krankh.*, 1910, B. I, p. 383.
- (19) LOHNSTEIN. *Monatsber. f. Urologie*, 1904, *cit. Ibid.*, 1910, B. I, p. 383.
- (20) LANGER and JACOBSON. *Berlin dermat. Ges.* 8/7-24, *Zentr. f. H. and G.*, 1924, B. 14, p. 25.
- (21) STAS. *Compt. rend. soc. chim.*, B. 73, p. 998 (*Chem. Zentr. bl.*, 1871, p. 710).
- (22) GROS. *Münch. med. W.*, 1911, p. 2659.
- (23) v. NEBRGAARD. *Klin. W.*, 1923, p. 1699; *A. f. exp. Pharm. and Path.*, 1923, B. 100, p. 162.
- (24) HAXTHAUSEN. *Hosp. tid.*, 1921, p. 394.
- (25) EISENBERG and OKÓLSKA. *Zentr. f. Bakteriologie*, 1913, B. 69, p. 312.
- (26) TH. HANSEN. *Hosp. tid.*, 1921, p. 657.